Remarks

Claims 1-7 and 10-21 were pending in the subject application. By this Amendment, the applicants have amended claims 1 and 4-7, added new claims 22 and 23 and cancelled claims 10, 11 and 16-21 as being drawn to non-elected subject matter. Support for the claim amendments can be found in the specification as originally filed. No new matter has been added by these amendments. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-7, 12-15, 22 and 23 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

The amendments set forth herein have been made in an effort to lend greater clarity to the claimed subject matter and to expedite prosecution. These amendments should not be taken to indicate the applicants' agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

The applicants would like to bring to the Examiner's attention a Supplemental Information Disclosure Statement listing references for consideration in the prosecution of the subject application that is being submitted in conjunction with the filing of this Amendment. The applicants respectfully request that the references be considered and made of record by the Examiner in the subject application.

Initially, the Office Action states that there are sequences in the figures that are not accompanied by the required reference to the relevant sequence identifiers. Attached herewith are Replacement Figures 1-4 and 6-9 that include the sequence identifiers for each of the sequences. Also attached are Annotated Figures 1-4 and 6-9.

Claims 6 and 7 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The applicants respectfully traverse this ground for rejection to the extent that it might be applied to the claims as amended herein.

The applicants appreciate the Examiner's careful review of the claims. The claims have been amended herein to address the issues raised by the Examiner.

Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph.

Claims 1-7 and 12-15 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The applicants respectfully traverse this ground for rejection because the skilled artisan could readily, and without undue experimentation, practice the full scope of the invention as currently claimed.

The Office Action states that Ichikawa *et al.* provide evidence that lactic acid bacteria (LAB) can activate the intestinal immune system by a TLR9-independent mechanism, and that, therefore, expression of a TLR receptor in intestinal lymphoid tissue is not sufficient to predict activation of the intestinal immune system. The Office Action further states that, based on the evidence provided by Fukata *et al.*, the skilled artisan, at the time of filing, could not accurately predict whether activation of TLR9, or another TLR, in the screening assays would result in activation of the intestinal immune system.

The applicants respectfully disagree with this characterization of the state of the art. The evidence provided by Ichikawa *et al.* only indicates the possibility of a TLR9-independent mechanism activating the intestinal immune system. This does not negate the association between the activation of TLR9 (in a cell-based assay) and the activation of the intestinal immune system. In other words, the possibility that there may be more than one mechanism for activating the immune system does not change the fact that the current inventors have discovered that activation of TLRs is associated with intestinal immunostimulation. Also, Fukata *et al.* only indicate that the expression, localization and function of individual TLRs is "unclear." Such ambiguous speculation is inadequate as a basis to deny the association between activation of TLRs in cell-based assays and activation of intestinal immune system as established and claimed by the current applicants.

Attached herewith are two references (*FEMS Immunol Med Microbiol.* 2005 June 1; 44(3):283-288 and *Vet Res.* 2006 Nov-Dec; 37(6):791-812. Epub 2006 Sept 15) with post-filing date data by the inventors of the present application. In the *FEMS Immunology and Medical Microbiology* reference, it was demonstrated that the swine TLR2-expressing transfectant can bind not only zymosan from yeast cell wall components but also intact lactic acid bacteria, resulting in the activation of nuclear factor –κB (NF- κB), which is known as a transcriptional factor activated when

immune proteins are produced. This result shows that swine TLR2-expressing transfectants can be used for the primary screening of immunobiotic microorganisms.

In the *Veterinary Research* reference, experimental data show that TLR2 and TLR9 allow mesenteric lymph nodes and ileal Pps to respond to a variety of bacterial components immediately after birth, thereby providing newborns with a host defense system. Specifically, Figure 1 shows that TLR2 and TLR9 are strongly expressed in ileal Peyer patches (Pps) and mesenteric lymph nodes (MLNs) of swine, which are gut-associated lymphoid tissues. Figure 2 shows immunofluorescent localization of TLR2 and TLR9 expression in longitudinal sections of newborn swine MLN, indicating that TLR2 and TLR9 are strongly expressed. Figure 5C shows that CpG2006 binds to TLR9. Figure 7 shows mitogenic activity of CpG2006 and zymosan towards newborn swine ileal Pps and MLN. Immunity is increased by the proliferative effect of lymphocytes. TLR9-mediated intestinal immune system stimulation is suggested by the fact that CpG2006 is a strong ligand ofTLR9. This can also be seen from Figure 8, which shows an analysis of cytokine mRNA expression in swine newborn ileal Pps and MLN.

As established by these references, there is an association between the activation of TLRs in a cell-based assay and the activation of the intestinal immune system. Accordingly, the skilled artisan, having the benefit of the applicants' disclosure can readily, and without undue experimentation, practice the claimed invention.

As a further aspect of the enablement rejection, the Office Action states that the claimed method is only enabled for the use of naturally-occurring mammalian TLRs. In order to expedite prosecution, the claims have been amended herein to recite the use of naturally-occurring mammalian TLRs, thereby rendering moot this aspect of the enablement rejection.

In a final aspect of the enablement rejection, the Office Action suggests amending the claims to recite the use of an "isolated" cell. The claims have been amended herein in accordance with the Examiner's suggestion.

For an invention to be enabled under the first paragraph of §112, the specification need only teach a person of ordinary skill in the art "how to make" and "how to use" the invention. It should also be noted that the requirement for some experimentation and/or screening does not necessarily make a claim non-enabled. "Enablement is not precluded by the necessity for some experimentation

such as routine screening. . . A considerable amount of experimentation is permissible, if it is merely routine . . ." (emphasis added). *In re Wands,* 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

In accordance with the present invention it has been established that there is an association between the activation of TLRs in a cell-based assay and the activation of the intestinal immune system. As discussed above, the assay as currently claimed, can be readily practiced by the skilled artisan without undue experimentation. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Claims 1-7 and 12-15 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The applicants respectfully traverse this ground for rejection to the extent that it might be applied to the claims now presented for examination.

The Office Action states that the specification provides a representative number of species to describe the genus of "intestinal tract tissue-expressed Toll-like receptor" with respect to naturally-occurring mammalian sequences that would be active in a cell-based assay, but fails to describe or teach any mutant TLRs that differ from a naturally-occurring sequence and retains the cell-based activity of the parent polypeptide. In order to expedite prosecution, the claims have been amended herein to recite the use of naturally-occurring mammalian TLRs.

Accordingly, the applicants respectfully request reconsideration and withdrawal of the written description rejection under 35 U.S.C. §112, first paragraph.

Claims 1-5, 12, 13 and 15 have been rejected under 35 U.S.C. §102(b) as being anticipated by Akira *et al.* (WO 02/06482). The applicants respectfully traverse this ground for rejection because the cited reference does not disclose or suggest each and every element of the claimed invention.

This rejection arises because crucial claim limitations have, improperly, not been given patentable weight. Specifically, the Office Action states that the recitation of "for assessing whether a test sample activates the intestinal tract immune system" in the preamble of the claims is interpreted as an intended use and bears no patentable weight to distinguish the claimed method over one from the prior art. The Office Action also states that the "judgment" step in the concluding statement of claim 1 does not patentably distinguish the instant screening method from prior art screening methods wherein test samples that activate a TLR are identified (for a different purpose).

Upon discounting these aspects of the claimed invention, the Office Action states that Akira *et al.* teach the other steps of the claimed assay and, thus, anticipate claim 1.

The analysis as set forth in the Office Action, in which crucial claim limitations are ignored, is contrary to the applicable portions of the Manual of Patent Examining Procedures (MPEP), as well as relevant case law, and is inconsistent with other portions of the Office Action.

MPEP §2111.02 states:

> The determination of whether a preamble limits a claim is made on a case-by-case basis in light of the facts in each case; there is no litmus test defining when a preamble limits the scope of a claim. *Catalina Mktg. Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808, 62 USPQ2d 1781, 1785 (Fed. Cir. 2002).
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> "[A] claim preamble has the import that the claim as a whole suggests for it." *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620, 34 USPQ2d 1816, 1820 (Fed. Cir. 1995). "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999). See also *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003)(In considering the effect of the preamble in a claim directed to a method of treating or preventing pernicious anemia in humans by administering a certain vitamin preparation to "a human in need thereof," the court held that the claims' recitation of a patient or a human "in need" gives life and meaning to the preamble's statement of purpose.). (emphasis added)
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> a "preamble may provide context for claim construction, particularly, where that preamble's statement of intended use forms the basis for distinguishing the prior art in the patent's prosecution history." *Metabolite Labs., Inc. v. Corp. of Am. Holdings*, 370 F.3d 1354, 1358-62, 71 USPQ2d 1081, 1084-87 (Fed. Cir. 2004).
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> See also *Catalina Mktg. Int'l v. Coolsavings.com, Inc.*, 289 F.3d at 808-09, 62 USPQ2d at 1785 ("[C]lear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim

> limitation because such reliance indicates use of the preamble to define, in part, the claimed invention.

From these passages in the MPEP it is clear that preamble's statement of intended use must be given patentable weight when, as in this case, it gives "life, meaning, and utility" to the claim, and when it helps to distinguish from the prior art.

The Metabolite Labs case cited above provides important insight into the proper interpretation of both the preamble of the current applicants' claim 1, as well as the "judgment" step. The "judgment" step in the current applicants' claims corresponds to the "correlating" step in the Metabolite Labs assay.

With regard to the Metabolite Labs case the MPEP states:

> The patent claim at issue was directed to a two-step method for detecting a deficiency of vitamin B or folic acid, involving (i) assaying a body fluid for an "elevated level" of homocysteine, and (ii) "correlating" an "elevated" level with a vitamin deficiency. 370 F.3d at 1358-59, 71 USPQ2d at 1084. The court stated that the disputed claim term "correlating" can include comparing with either an unelevated level or elevated level, as opposed to only an elevated level because adding the "correlating" step in the claim during prosecution to overcome prior art tied the preamble directly to the "correlating" step. 370 F.3d at 1362, 71 USPQ2d at 1087. The recitation of the intended use of "detecting" a vitamin deficiency in the preamble rendered the claimed invention a method for "detecting," and, thus, was not limited to detecting "elevated" levels. *Id.*

It is apparent from the analysis of the claims in the Metabolite Labs case that both the preamble and the "correlating" (e.g. judgment) step were not ignored or discounted; rather, these aspects of the claim were treated as critical claim limitations that were used both to distinguish the invention from the cited art as well as to establish the scope of the claim for infringement purposes. In this regard, the current case is analogous to the Metabolite Labs case such that the preamble and the judgment step of the applicants' claims must be given patentable weight.

The importance of the preamble of the current applicants' claim is acknowledged in the outstanding Office Action where, at page 4, it is stated:

> The claims recite the intended use of "for assessing whether a test sample activates the intestinal tract immune system". Thus, for purposes of enablement, the specification must enable the skilled artisan to practice the claimed method such that

> it results in assessment of intestinal tract immune system activation in response to a test sample.

Certainly, there is no basis in law or logic for emphasizing this claim limitation for purposes of enablement but then ignoring it for purposes of distinguishing from the prior art.

It is basic premise of patent law that, in order to anticipate, a single prior art reference must disclose within its four corners, each and every element of the claimed invention. In *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), the court stated:

> Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Connell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference. *SSIH, supra*; *Kalman [v. Kimberly-Clarke*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

Akira *et al.* do not teach that the activation of TLRs in a cell-based assay is associated with the activation of the intestinal immune system. Thus, Akira *et al.* do not provide "a method for assessing whether a test sample activates the intestinal tract immune system" as is required by the applicants' claims. Nor do Akira *et al.* disclose or suggest an assay wherein the end result involves identifying test samples that activate the intestinal tract immune system. The applicants' claimed assay is an important contribution to the art that is not disclosed or suggested by the cited reference.

Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §102(b) based on the Akira *et al.* reference.

Claims 1-5, 12, 13 and 15 have been rejected under 35 U.S.C. §102(e) as being anticipated by Lipford *et al.* (WO 2004/026888). The applicants respectfully traverse this ground for rejection because the cited reference does not disclose or suggest each and every element of the claimed invention.

Lipford *et al.* do not teach that the activation of TLRs in a cell-based assay is associated with the activation of the intestinal immune system. Thus, Lipford *et al.* do not provide "a method for

assessing whether a test sample activates the intestinal tract immune system" as is required by the applicants' claims. Nor do Lipford *et al.* disclose or suggest an assay wherein the end result involves identifying test samples that activate the intestinal tract immune system. The applicants' claimed assay is an important contribution to the art that is not disclosed or suggested by the Lipford *et al.*.

Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §102(b) based on the Lipford *et al.* reference.

Claims 6 and 7 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Akira *et al.* (WO 02/06482) as applied to claim 5 above, and further in view of Kitazawa *et al.* (2003, *International Journal of Food Microbiology*, 85(1-2):11-21). The applicants respectfully traverse this ground for rejection because the cited references, either taken alone or in combination, do not disclose or suggest the applicants' advantageous method for identifying immunostimulatory microorganisms.

As discussed above, the Akira *et al.* reference does not teach or suggest the applicants' unique and advantageous method for identifying microorganisms that stimulate an immune response in the intestines. The Kitazawa *et al.* reference does not cure the aforementioned shortcomings of the primary Akira *et al.* disclosure, nor does it supply any teachings that, even in combination with the Akira *et al.* reference, would make obvious the subject matter of claims 6 and 7 as amended herein.

The Office Action acknowledges that Akira *et al.* do not teach the additional step of claim 6 wherein a microorganism is mixed with a dietarily acceptable carrier, or the additional limitation of claim 7 that the microorganism is a "lactic acid bacterium." The Office Action states, however, that it would have been obvious to perform the screening method as taught by Akira *et al.*, but to substitute an extract from the microorganism (L. bulgaricus) taught by Kitazawa *et al.* for the extract from the microorganisms (bacteria in general) taught by Akira *et al.*, and to further mix a microorganism assessed to activate the Toll-like receptor with a dietarily acceptable carrier (acceptable at least to mice) taught by Kitazawa *et al.*

The applicants respectfully submit that this combination of references could only have been arrived at through the use of impermissible hindsight reconstruction of the prior art. Hindsight reconstruction of the prior art cannot support a §103 rejection, as was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969).

In any event, the claims have been amended herein to eliminate any ambiguity that may have contributed to the interpretation of the claims upon which this obviousness rejection has been made. Also, new claims have been added to which this combination of references would clearly not be applicable.

It is well established in the patent law that the mere fact that the purported prior art could have been modified or applied in some manner to yield an applicant's invention does not make the modification or application obvious unless "there was an apparent reason to combine the known elements in the fashion claimed" by the applicant. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ (2007). Furthermore, an applicant's invention is not "proved obvious merely by demonstrating that each of its elements was, independently, known in the (purported) prior art." *Id.* In this case, the applicants respectfully submit that there is no reason to modify the cited references to arrive at the current invention and, thus, there is no *prima facia* case of obviousness.

Specifically, the cited references do not provide a method for identifying microorganisms that stimulate the intestinal immune response. Without the knowledge of how to select microorganisms that stimulate the intestinal immune system, there would be no reason to use the selected microorganisms in the preparation of a composition that stimulates the intestinal immune system as claimed by the current applicant. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) based on Akira *et al.* In view of Kitazawa *et al.*

Claims 6 and 7 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Lipford *et al.* (WO 2004/026888) as applied to claim 5 above, and further in view of Kitazawa *et al.*). The applicants respectfully traverse this ground for rejection because the cited references, either taken alone or in combination, do not disclose or suggest the applicants' advantageous method for identifying immunostimulatory microorganisms.

As discussed above, the Lipford *et al.* reference does not teach or suggest the applicants' unique and advantageous method for identifying microorganisms that stimulate an immune response in the intestines. The Kitazawa *et al.* reference does not cure the aforementioned shortcomings of the

primary Lipford *et al.* disclosure, nor does it supply any teachings that, even in combination with the Lipford *et al.* reference, would make obvious the subject matter of claims 6 and 7 as amended herein.

Specifically, the cited references do not provide a method for identifying microorganisms that stimulate the intestinal immune response. Without the knowledge of how to select microorganisms that stimulate the intestinal immune system, there would be no reason to use the selected microorganisms in the preparation of a composition that stimulates the intestinal immune system as claimed by the current applicant. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) based on Lipford *et al.* In view of Kitazawa *et al.*

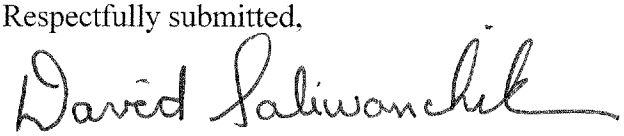
Accordingly, the applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a).

In view of the foregoing remarks and the amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Replacement Figures 1-4 and 6-9
Annotated Copy of Figures 1-4 and 6-9
Tohno *et al.* (2005)
Tohno *et al.* (2006)
Supplemental Information Disclosure Statement with references